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NOVEL LEWIS ACID-CATALYZED REARRANGEMENT OF A SUGAR-BASE HYBRID TO AFFORD AN ANHYDRONUCLEOSIDE

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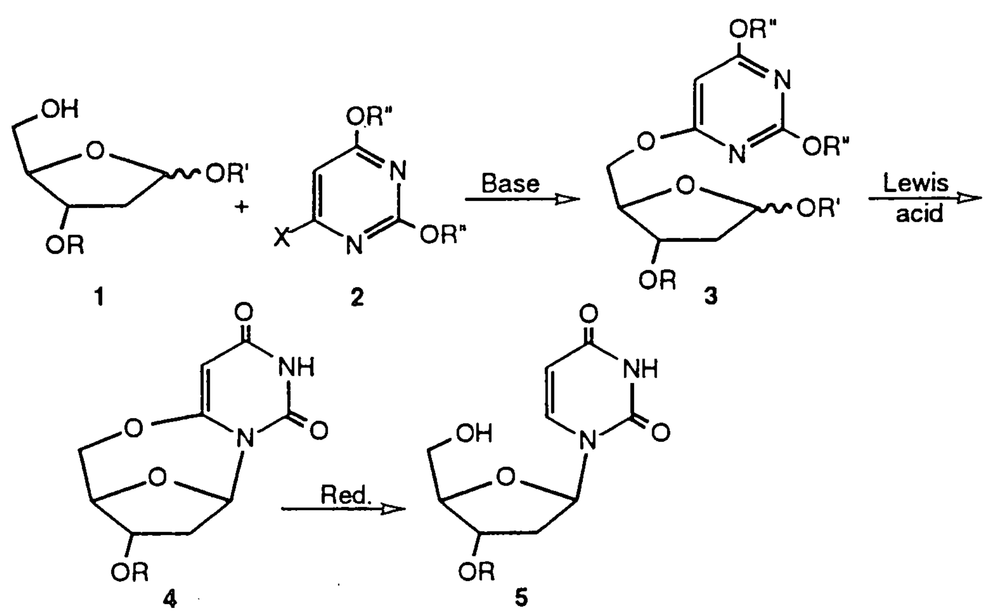
Michael E. Jung,*[1] Claire Castro,[2] and Saeed I. Khan[3]
Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095-1569

ABSTRACT: Treatment of the sugar-base hybrid **9** with boron trichloride at low temperature for 40 h affords the 6,3'-anhydro-2'-deoxyuridine **10** in 40% yield (80% based on recovered **9**) via a novel structural rearrangement.

During the course of studies aimed at developing an intramolecular Vorbrüggen coupling of sugar-base hybrids joined at the 5-position of the sugar and the 2-position of the base to generate, after hydrolysis, only the desired β-anomers of 2'-deoxynucleosides,[4,5] we examined the preparation and cyclization of the sugar-base hybrid **3** in which the deoxyribose component **1** was added to a 6-halo-2,4-dialkoxypyrimidine **2**. We hoped that intramolecular coupling could be effected in the presence of a suitable Lewis acid catalyst to produce, after aqueous workup, the 6,5'-anhydro barbituric acid nucleoside **4**.



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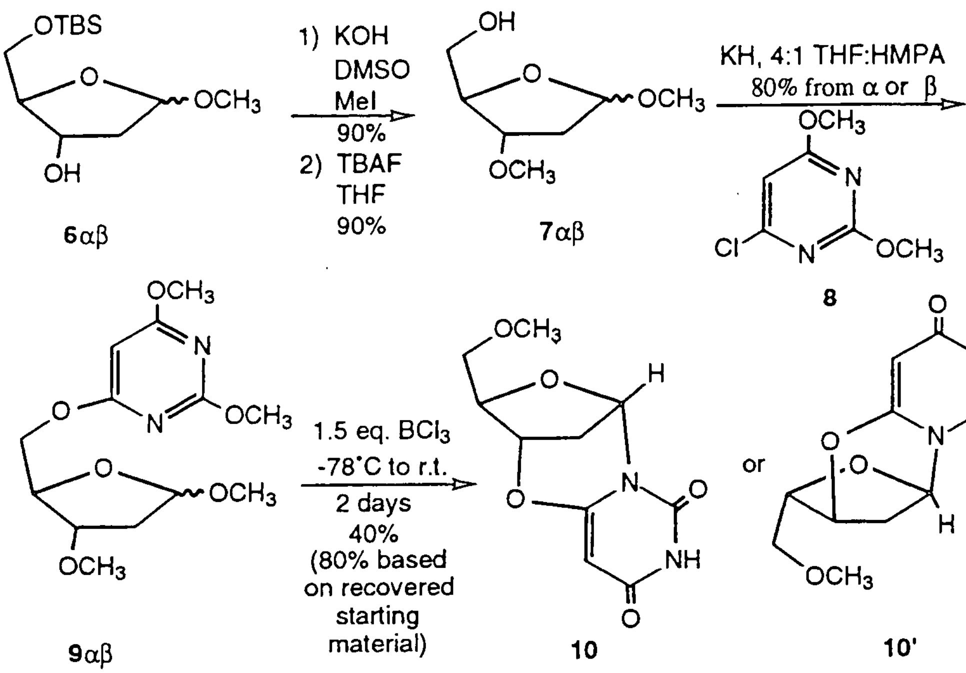
These are important modified nucleosides themselves as well as potential intermediates for the synthesis of normal pyrimidine nucleosides. Reduction (or hydrolysis-reduction) of the vinyl ether of **4** could give the desired 2'-deoxyuridine **5**.[6] We now report a novel Lewis acid-catalyzed rearrangement of a sugar-base hybrid such as **3** which produced an unexpected 6,3'-anhydronucleoside in fair yield.



The two O^6,5'-bridged precursors **9αβ** were prepared separately from the known[7] methyl ribosides **6αβ** as follows. Methylation (KOH, DMSO, MeI, 90%) afforded the methyl ether which was desilylated (TBAF, THF, 90%) to give each of the methyl ribosides **7αβ**.[8] Formation of the anion with base and addition of the commercially available 6-chloro-2,4-dimethoxypyrimidine **8** gave the desired sugar-base hybrids **9αβ**. A variety of Lewis acids (TMSOTf, TBSOTf, $SnCl_4$, $TiCl_4$, Et_2AlCl) were ineffective at promoting

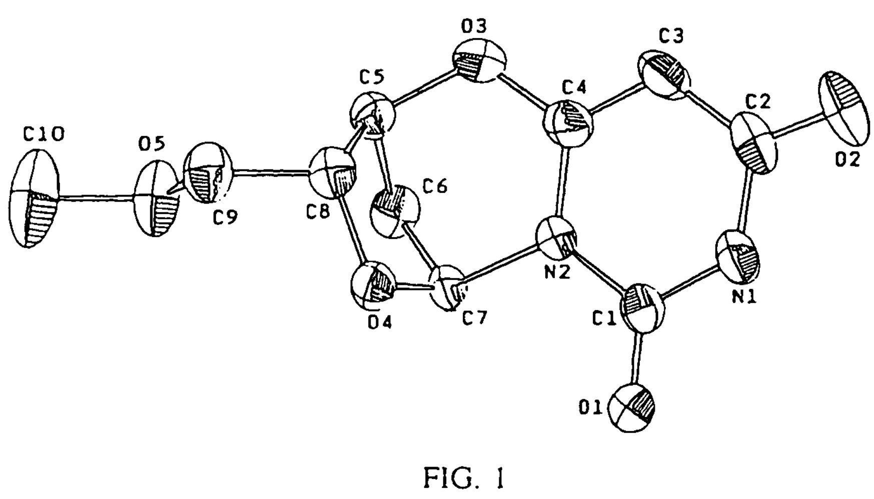
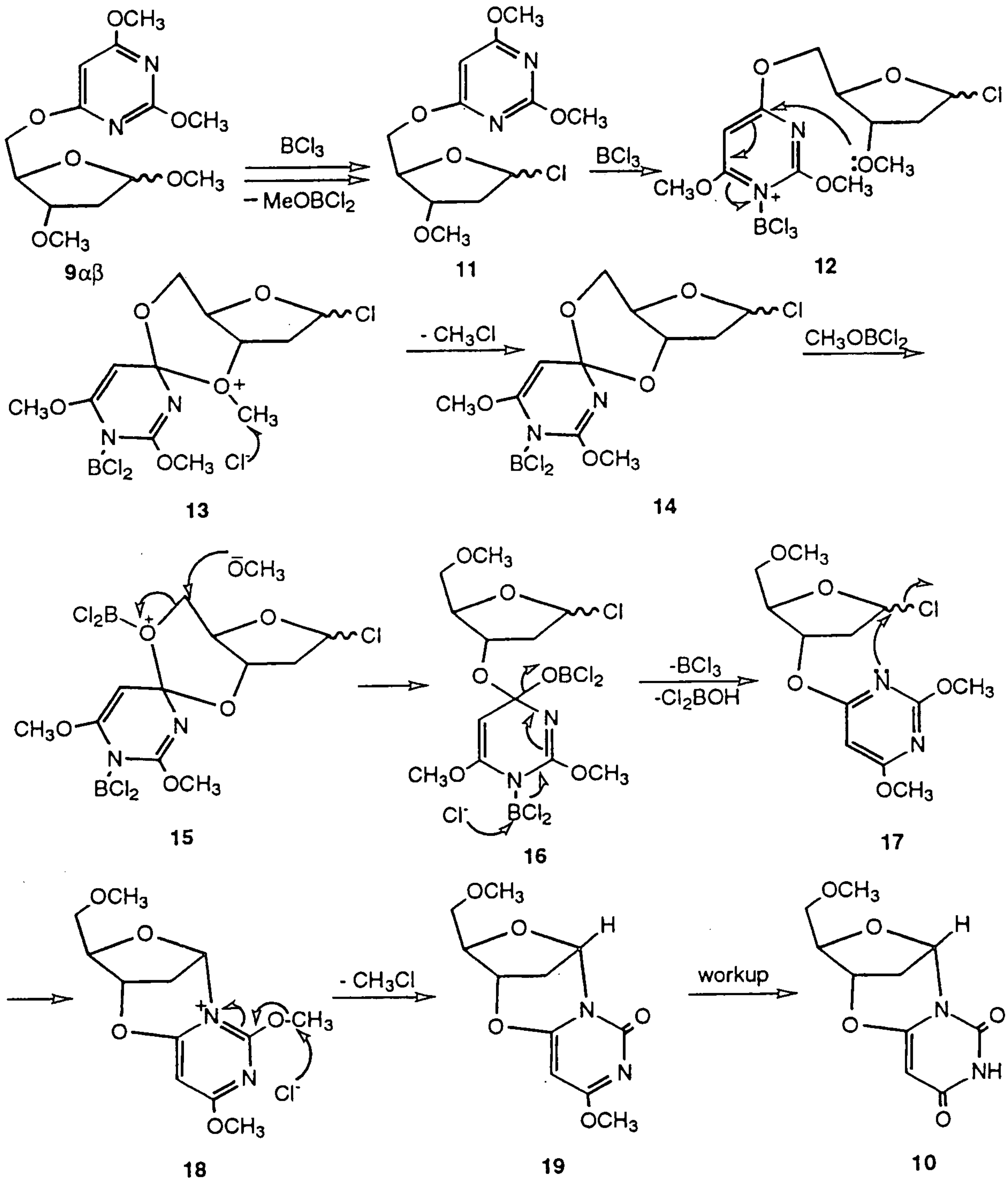


FIG. 1


OCH3
N
O
OCH3
O
OCH3
OCH3
9αβ
BCl3
- MeOBCl2
Cl
11
BCl3
CH3O
N+
BCl3
:OCH3
OCH3
12
13
O+
CH3
BCl2
Cl-
- CH3Cl
14
CH3OBCl2
15
ŌCH3
Cl2B
16
OBCl2
-BCl3
-Cl2BOH
17
18
- CH3Cl
19
H
workup
NH
10

Scheme

cyclization. Anomerization and/or hydrolysis of the methyl riboside were the only processes observed. However, when either anomer of 9αβ was treated with boron trichloride, the crystalline anhydro compound **10** was isolated in 40% yield along with 50% of recovered anomerized starting material and some minor unidentified adducts. The surprising structure of **10** was suggested by its ^{1}H NMR spectrum which showed the 3'-proton at low field [δ 5.05 (1H, d, J = 0.8, 2.9 Hz] and the 5'-protons at much higher field [δ 3.57 (1H, dd, J = 3.4, 10.9 Hz) and δ 3.39 (1H, dd, J = 4.6, 10.8 Hz)], which implied that the substituent on the 3'-oxygen was electron withdrawing while that on the oxygen at 5' was not. The structure was proven conclusively by an x-ray crystal structure (Figure 1). Unfortunately, the poor quality of the crystal did not allow us to identify which enantiomeric form of **10** had been produced. However the compound isolated was optically active $[\alpha]_D^{25}$ = +21.3 (c 1.4, $CHCl_3$) and we believe that **10** is a more reasonable structure than **10'** because that structure would require inversions at both C-3 and C-4, which would be very difficult to explain.

The probable mechanism for the formation of **10** is shown in the Scheme, namely an intramolecular transfer of the base to the 3'-oxygen followed by cyclization. Conversion of the anomeric methoxyl group to chloride **11** presumably occurs first. Activation of the pyrimidine ring by boron trichloride **12** leads to attack by the 3' methoxy to afford the salt **13** which can lose methyl chloride to generate the spirocyclic orthoamide **14**. Activation of the bridging oxygen with methoxyboron dichloride would give an intermediate salt **15** which would react with methoxide to afford the 5'-methoxy compound **16**. Rearomatization of the pyrimidine would produce the sugar-base hybrid linked at the 3'-position of the sugar **17**. Final intramolecular glycosidation would give **18** which on loss of methyl chloride would furnish the methyl imidate of the product **19** or its regioisomer.[9] Hydrolysis on workup would then produce the observed product **10**. There are other possible pathways, e.g., formation of the 5'-chloro compound which could afford the 5'-methoxy compound via an internal displacement of the type suggested by Horowitz.[10] Obviously the reaction could also take place by an intermolecular process although that seems less likely.

In summary we have shown that a O^6,5'-bridged sugar-base hybrid **8** is converted with boron trichloride into the 6,3'-anhydro-2'-deoxyuridine **9** in 40% yield (80% based on recovered starting material) via an unusual structural rearrangement. We will report soon the use of 3'-linked base-sugar hybrids for the stereospecific preparation of only the desired β-anomers of 2'-deoxynucleosides by an internal Vorbrüggen process.[9]

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1) American Chemical Society Arthur C. Cope Scholar, 1995.

2) UCLA BASF Fellow, 1990; UCLA Mentorship Awardee, 1992. Current address: Department of Chemistry, University of San Francisco, San Francisco, CA 94117-1080.

3) To whom questions about the x-ray structure determination should be addressed.

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5) For other examples of intramolecular Vorbrüggen couplings, see: a) Sujino, K.; Sugimura, H. *J. Chem. Soc., Chem. Commun.* **1994**, 2541; *Tetrahedron Lett.* **1994**, *35*, 1883; *Chem. Lett.* **1993**, 1187. b) Sugimura, H.; Motegi, M.; Sujino, K. *Nucleosides Nucleotides* **1995**, *14*, 413. c) Mizuno, Y.; Kaneko, C.; Oikawa, Y.; Ikeda, T.; Itoh, T. *J. Am. Chem. Soc.* **1972**, *94*, 4737. d) Mizuno, Y.; Kaneko, C.; Oikawa, Y. *J. Org. Chem.* **1974**, *39*, 1440. e) El Subbagh, H. I.; Ping, L.-J.; Abushanab, E. *Nucleosides Nucleotides* **1992**, *11*, 603. f) Chemla, P. *Tetrahedron Lett.* **1993**, *34*, 7391.

6) Several methods exist for the hydrogenolysis of phenols to give the corresponding arenes. For an example, see: Musliner, W. J.; Gates, J. W., Jr. *J. Am. Chem. Soc.* **1966**, *88*, 4271.

7) Ichikawa, Y.; Kubota, H.; Fujita, K.; Okauchi, T.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 845.

8) The procedure for forming **7αβ** involved addition of powdered KOH to a solution of the methyl ribosides **6αβ** and MeI in DMSO and stirring at ambient temperature for 5h. Desilylation was effected by the normal technique (TBAF and the silyl ether were stirred together in THF for 1.5 h at ambient temperature). The proton NMR spectra of **7αβ** corroborate their structures, e.g., the OH proton of **7β** is a dd (J = 9, 3.3 Hz) coupled to the two C5 protons, and therefore no shift of the TBS group from the oxygen at C3 to that at C5 occurred during the base-promoted methylation. We thank the referee for suggesting that possibility.

9) Such intramolecular Vorbrüggen reactions from the 3'-position to the anomeric center proceed in reasonable yields. a) Xia, X.; Wang, J.; Hager, M. W.; Sisti, N.; Liotta, D. C. *Tetrahedron Lett.* **1997**, *38*, 1111. b) Jung, M. E.; Castro, C.; Yang, E. unpublished results.

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